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Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 02D-0232; Draft Guidance, "International Conference on Harmonization; Draft Guidance on S7B Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals". ***Reference: 67 Federal Register 40950 (June 14, 2002)***

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. We are a leader in the research and development of innovative therapies for cardiovascular, metabolic and infectious diseases, neurological disorders, and oncology. In 2001 alone, Bristol-Myers Squibb dedicated $2.1 billion for pharmaceutical research and development activities. The company has nearly 6,000 scientists and doctors committed to discover and develop best in class therapeutic and preventive agents that extend and enhance human life. Our current pipeline comprises more than 50 compounds under active development.

For these reasons, we are very interested in and well qualified to comment on this ICH Step 2 draft guidance on Safety Pharmacology studies to assess the potential for delayed repolarization by human pharmaceuticals.

Summary of Comments

Bristol-Myers Squibb appreciates the ICH efforts to develop a guidance document for safety pharmacology studies in assessing the potential for human pharmaceuticals to influence myocardial repolarization. It does, however, have several comments regarding the need for clarification and timeline considerations. The guideline should discuss its applicability to drugs already in clinical development as well as new chemical entities. In addition, the document should state whether in vitro assays must be conducted in compliance with GLP and if so, at what stage of the filing process GLP studies are required (e.g. for IND or NDA). The guideline also should clarify whether reference to GLP in the S7A safety pharmacology ICH Harmonized Tripartite Guideline applies to the enhanced or follow-up in vivo testing described in this

guideline. Finally, the guideline should discuss criteria for exempting drugs from GLP testing requirements at the time of its implementation. For example, would late stage clinical development programs be exempted? This might avoid potential registrational delays and confusion on the part of both FDA reviewer's and registrants.

There is concern that the guidance will increase the need for testing at a time of constrained resources. Currently, there are only a very limited number of contract research organizations prepared to perform this testing in compliance with rigorous scientific standards and Good Laboratory Practices (GLP). Consequently, time is needed for general implementation of the guideline.

The guideline also fails to acknowledge the value of extensive nonclinical testing in mitigating the effort required during clinical development. Rigorous nonclinical testing, such as that prescribed by the guideline, and demonstrated safety in early clinical development should obviate the need for extensive cardiovascular testing in later stages of clinical development. The guideline should be revised to include a discussion on the potential positive impact of nonclinical studies on clinical development.

The in vitro aspects of the ICH S7B step 2 draft guideline offer useful general guidance on testing strategies for assessment of the potential for QT effects. The guideline considers in vitro ionic current assays and action potential duration assays to be acceptable and sufficient, when done in conjunction with in vivo electrophysiology studies, for assessing the potential of pharmaceuticals to produce delayed ventricular repolarization. The guideline correctly recognizes cardiac IKr (HERG) as the primary culprit ion channel target for pharmaceuticals known to cause delayed ventricular repolarization and appropriately recommends that compounds be tested for activity against either endogenous IKr or recombinant HERG currents.

However, the guideline suggests that compounds be tested in vitro over potentially very broad dosage ranges, which may not be appropriate for some compounds such as that known to have low therapeutic plasma concentrations. Moreover, despite recommending testing up to potentially high doses (solubility limits), the guideline states that any non-antiarrhythmic pharmaceutical that blocks repolarizing ionic currents (or prolongs action potential duration) should be considered to pose a potential risk to humans. Some effort should be given to establishing guidelines for interpreting in vitro ion channel potency or action potential data, particularly if compounds must be tested at high concentrations.

The guideline correctly suggests that multiple action potential parameters in addition to action potential duration, such as maximal rate of depolarization, can be useful in assessing the electrophysiological action of test substances in the heart. However, since the clinical implications of some action potential effects are not well understood (e.g. APD50 shortening or prolongation, APD90 shortening, Vmax increases, action potential amplitude changes), the guideline should address how this data might be interpreted by a regulatory agency. The guideline suggests that a positive signal from the pharmacologic/chemical class is generated when a test substance belongs to a group of pharmacological agents that are known to prolong QT interval in the clinic. Although a number of problem classes are obvious (e.g. quinolone

antibiotics, tricyclic antidepressants), the guideline should provide some guidance on which classes are considered problematic. The guideline recommends testing metabolites in in vitro assays but does not specify criteria for considering which metabolites (ie- % of parent compound accumulated) should be tested.

The guideline indicates that the in vivo testing strategy is pragmatic and based on currently available information. However, implementation of this guideline is not currently practical considering the large numbers of new drug candidates expected to generate positive initial signals and the limited number of testing laboratories with fully validated test systems.

The guideline suggests that conscious non-rodent instrumented models will be needed for enhanced or follow-up in vivo testing. However, these models have not been validated with non-antiarrhythmic agents known to cause QT prolongation and there is likely to be a considerable period before the industry has established reliable models in conscious animals that detect minor changes in QT interval. The guideline should be revised to recognize this issue and indicate that anesthetized non-rodent models may be an acceptable standard.

Decisions to proceed with enhanced in vivo safety pharmacology testing prior to first administration in humans (FIM) should be made case by case based on considerations for therapeutic indication, chemical structure, in vitro and in vivo safety pharmacology information, and toxicology, toxicokinetic, and pharmacodynamic information. This is consistent with the S7A safety pharmacology ICH Harmonized Tripartite Guideline (section 2.9) and is applicable for this guideline.

Complete metabolic and toxicokinetic data in multiple species may not be available to aid in the design of preclinical safety pharmacology studies. This potential limitation was recognized in the S7A ICH Harmonized Tripartite Guideline, and comparable language should be added to this guideline.

In summary, although Bristol-Myers Squibb understands the basic principles and the key in vitro and in vivo assays recommended in the guideline, we believe that the guidelines could benefit from additional modifications as detailed below.

Specific Comments

In Vitro Testing

2.3.1 Recommended Nonclinical Testing Strategy

The guideline states: "the following information should generally be provided:
1. Evaluation of whether the test substance belongs to a pharmacological/chemical class known to prolong QT interval in humans" and "A positive signal from the pharmacological/chemical class is generated when the test substance belongs to a group of pharmaceuticals of which many, though not necessarily all, members have been shown to induce QT interval prolongation in humans."

Implementation of this aspect may be burdensome in those instances where a problem class is poorly defined or when the clinical data is misleading. For example, some pharmacologic agents are associated with QT prolonging risks not because they affect repolarizing currents but rather affect the metabolism of agents that are co-prescribed and that may inhibit HERG or other repolarizing currents. The guideline should reference those classes of agents that are considered to be problematic. The list would likely change with time but could be updated in subsequent releases of the guideline or in a web-based directory.
The guideline states: "Information from follow-up studies could be related to potency, slope of the dose response curve, or magnitude of the nonclinical response. Another application is to determine whether an apparent positive or equivocal signal in an assay is the result of an artifact. Follow-up studies are designed to address specific issues, and, as a result, various in vivo or in vitro study designs can be applicable" and "The design of follow-up studies in vitro can focus on issues such as activity of metabolites or inhibition of other channels not previously evaluated."

Implementation of this aspect may not obtain the intended result since the guideline does not provide any detail regarding when and what types of in vitro follow-up studies to conduct, interpretation of results from follow-studies, or circumstances where follow-up studies might be required.

2.3.3 Implications of Nonclinical Studies

The guideline states: "Any non-antiarrhythmic pharmaceutical that blocks repolarizing ionic currents (or enhances depolarizing currents), increases the cardiac action potential duration, prolongs the QT interval, or elicits arrhythmic events in nonclinical studies should be considered to pose a risk to humans, especially if in vivo effects occur at concentrations that are low multiples of the anticipated therapeutic plasma concentrations."

Implementation of this aspect may not obtain the intended result without well-defined guidelines for interpreting positive results. The guideline recommends testing agents at concentrations that may be in great excess (see comments under 3.1.2) of maximal therapeutic concentrations and therefore positive signals in in vitro assays could be irrelevant. Guidelines for interpreting results of in vitro assays should be more clearly defined.

3.1.1 Use of Positive Controls and Reference Compounds

The guideline states: "Positive control substances should be used to establish the sensitivity of in vitro preparations for ionic current or action potential duration assay. In the case of in vivo studies, positive control substances should be used to validate and define the sensitivity of the test system, but need not be included in every experiment."

Implementation of this aspect may be burdensome because, although positive controls and reference compounds should be and are used to validate in vitro testing systems (e.g. voltage-clamp assays on HERG-expressing cell lines), it would be impractical to run control compounds

with every test agent, particularly when compounds are evaluated in these assays during routine profiling in pre-clinical development. As is stated for in vivo testing, the guideline should state that positive controls need not be included in every experiment.

3.1.2 In Vitro Electrophysiology Studies

The guideline states: "Test substance concentrations for in vitro studies should span a broad range, covering and exceeding the anticipated maximal therapeutic plasma concentration. Ascending concentrations should be tested until a concentration-response curve has been characterized or physicochemical effects become concentration-limiting."

Implementation of this aspect may not obtain the intended result since no consideration is given to maximal plasma concentrations at therapeutic doses or to plasma protein binding. Although the data set for compounds known to prolong QT interval in the clinic is relatively small, there appears to be a good correlation between free plasma levels of drug and propensity for QT liability (Webster R, Leishman D and Walker D, Towards a drug concentration effect relationship for QT prolongation and torsades de pointes, Current Opinion in Drug Discovery & Development (2002) 5:1, 116-126). The guidelines should acknowledge this and reconsider the recommendation to test compounds to physicochemical limits.

The guideline states: "Because cardiac cells and tissues have limited capacity for drug metabolism, in vitro studies using the parent substance usually do not provide information on the potential effects of metabolites. When in vivo animal or clinical studies reveal QT interval prolongation that is not corroborated by in vitro studies using the parent substance, testing major metabolites in the in vitro test systems should be considered."

Implementation of this aspect may be burdensome because, although the suggestion for testing metabolites is a good one, no definition of "major metabolites' is given in the guideline. The guideline should attempt to clarify the lower limit of what may be considered a significant metabolite (e.g. 10% of parent levels).

3.2.2 In Vitro Action Potential Duration Assays

The guideline states: "Parameters that provide useful information for QT interval prolongation and related proarrhythmic potential of a test substance include action potential duration (APD) at specific degrees of repolarization, e.g., action potential duration at 90% repolarization (APD90). Changes in other action potential parameters, including resting membrane potential, action potential amplitude, and maximum rate of depolarization (Vmax), can also be useful in assessing the electrophysiological action of a test substance on the heart."

Implementation of this aspect may not obtain the intended result since the clinical implications of changes in some action potential parameters are not well understood (e.g. APD50 shortening or prolongation, APD90 shortening, Vmax increases, action potential amplitude changes, combined Vmax and APD effects). In addition, there is little data and no consensus regarding when an effect should be considered significant or how the magnitude of effects on even well-defined

action potential parameters translates from in vitro action potential to pre-clinical or clinical ECG studies. Since the guidance was developed to "protect clinical trial participants and patients receiving marketed products from delayed repolarization-associated ventricular tachycardia, torsade de pointes, and lethal arrhythmia resulting from administration of pharmaceuticals" and to "provide general principles and information on currently available nonclinical methodologies to identify the potential hazard and assess the risk of QT interval prolongation by a pharmaceutical" perhaps recommendations for in vitro action potential assays should refer only to measurements that would likely produce delayed ventricular repolarization and define significance levels.

No Reference to Good Laboratory Practices

The guideline should include recommendations for whether the suggested in vitro assays should be conducted in compliance with the Good Laboratory Practice Regulations. Implementation of GLP assays would be burdensome if required at all stages of compound development/regulatory filing and it is suggested that GLP assays not be required until NDA filing. Timelines for implementation of in vitro GLP assays, if required, should take into consideration the lack of GLP compatible patch-clamp electrophysiology software.

In Vivo Testing

Additional information is needed regarding the timing and applicability of the guideline.

An expected timeline is needed for general implementation of the guideline. In addition, guidance is needed regarding the extent of its applicability for drugs already in clinical development. This latter guidance should specifically address the impact of the stage of clinical development on testing requirements.

Implementation of the guideline is not currently practical.

In section 2.3.1 Recommended Nonclinical Testing Strategy, the guideline indicates that the testing strategy is pragmatic and based on currently available information. However, implementation of this guideline is not currently practical considering the large numbers of new drug candidates expected to generate positive initial signals and the limited number of testing laboratories with fully validated test systems. These considerations are discussed below in more detail.

The number of pharmacological/chemical classes containing drugs reported to produce QT prolongation is extensive and, according to the guideline, new drug candidates in these classes will require enhanced testing.[1]

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1 DePonti F., Poluzzi E., Montanaro N. (2001). Organizing evidence on QT prolongation and occurrence of *Torsades de Pointes* with non-antiarrhythmic drugs: a call for consensus. Eur. J. Clin. Pharmacol. 57:185-209.

The guideline requires that in vitro preparations be evaluated at increasing drug concentrations until a response is obtained. Maximum drug concentration is limited only by physical perturbations of system membranes/channel integrity or limitations of solubility. Consequently, a much greater number of drugs are likely to produce positive signals in the in vitro assays compared with the number currently producing positive responses at relevant therapeutic concentration ranges.

Pharmaceutical-industry laboratories do not have the capacity to conduct enhanced in vivo safety pharmacology studies for all of the drug candidates likely to require testing as a result of this guideline. In addition, there are only a small number of contract research organizations that perform enhanced safety pharmacology evaluations, and these organizations are generally not performing the testing with the degree of scientific rigor required to adequately demonstrate assay sensitivity and reproducibility.

Implementing the guideline without adequate time for laboratory development will have two deleterious consequences. First, it will delay the introduction of new drug candidates. Second, in some cases, it will force the production of poor quality, potentially misleading data.

Anesthetized non-rodent models should be considered an acceptable testing standard

The guideline suggests that conscious non-rodent instrumented models should be the standard for enhanced or follow-up in vivo testing and that anesthetized non-rodent models should be used in special circumstances. However, conscious non-rodent instrumented models have not been validated with non-antiarrhythmic agents known to cause QT prolongation and there is likely to be a considerable period before the industry has established reliable models in conscious animals that detect minor changes in QT interval. The guideline should be revised to recognize this issue and indicate that anesthetized non-rodent models may be an acceptable standard.

Enhanced in vivo safety pharmacology testing should not be required for all drugs demonstrating positive preclinical signals.

Decisions to proceed with enhanced safety pharmacology testing prior to first administration in humans (FIM) should be made on a case by case basis. This is consistent with the S7A safety pharmacology ICH Harmonized Tripartite Guideline (section 2.9) relative to cytotoxic agents and is applicable for this guideline. The decision to proceed should be based on considerations for therapeutic indication, chemical structure, in vitro and in vivo safety pharmacology information, and toxicology, toxicokinetic, and pharmacodynamic information. For example, enhanced testing based on a positive signal from an in vitro assay should not be required prior to FIM for terminal cancer patients if the potential for QT prolongation at therapeutic exposure levels is small, and if there are no additional warnings or signals that increase concern. In this case, delaying FIM to conduct additional safety pharmacology evaluations is inappropriate.

No Reference to Good Laboratory Practices

GLPs are not discussed in the guideline and registrants must assume that the discussion of GLPs in the S7A safety pharmacology ICH Harmonized Tripartite Guideline (section 2.11) extend to the S7B guideline. This should be clarified in relation to the enhanced or follow-up in vivo testing described in this guideline.

Complete metabolic and toxicokinetic data may not be available during early stages of development.

Strict interpretation of the guideline indicates that metabolic and toxicokinetic data in multiple species should be available to aid in the design of preclinical safety pharmacology studies. However, this information is generally incomplete during early stages of development. This potential limitation was recognized in the S7A safety pharmacology ICH Harmonized Tripartite Guideline, which states the following in section 2.2 General Considerations in Selection and Design of Safety Pharmacology Studies:

"During early development, sufficient information (e.g., comparative metabolism) may not always be available to rationally select or design the studies in accordance with the points stated above; in such circumstances, a more general approach in safety pharmacology investigations can be applied."

Comparable language should be added to this guideline to acknowledge this potential limitation.

2.3.1 Recommended Nonclinical Testing Strategy

The following two comments are directed at the bullets near the end of this section that list considerations for the design of enhanced or follow-up in vivo studies.

1.) The methods used to identify drug-related changes should be considered in the design phase of the study. This item is specified later in the guideline (section 3.1.3) and should also be included in section 2.1.3. The bulleted text used in section 3.1.3 ("data acquisition and analysis methods") is suitable for both sections.

2.) The bulleted text stating "use of adequate numbers of animals" should be qualified since strict adherence to statistical requirements can be impractical. The following should be added to the end of this bulleted text.

"(based on desired sensitivity and practical considerations)"

2.3.3 Implications of Nonclinical Studies

This section should indicate that positive signals early in preclinical testing may not necessitate rigorous ECG testing in later stages of clinical development (e.g., Phase IIb and III clinical trials) pending the results of thorough nonclinical investigations and earlier clinical trials.

3.4.1.1 Acquisition and Analysis of the QT Interval

1). The last sentence of the first paragraph reads "In all cases, the investigator should visually confirm the accuracy of a computer-measured QT interval." This could be taken out of context and misinterpreted to indicate that all QT interval data need to be recalculated manually. The investigator must review the computer generated data and make corrections as appropriate so the calculated data are not compromised in any way. However, manual recalculation of the data negates the advantages of automated data analyses. Further, the ability of the automated analyses system to accurately measure ECG waveform intervals must be examined prior to testing as a component of system validation. Once the system is validated, the investigator's responsibility is to ensure that subject specific waveform irregularities don't compromise the automated data analyses. The last sentence should be replaced with the following text.

"In all cases, the investigator should review ECG waveforms to ensure the adequacy of computer-measured QT interval data."

2.) The second paragraph implies that baseline data for vehicle-treated groups need not be considered in the evaluation. The text should be modified to indicate that statistical comparisons between drug-treated and vehicle-treated groups should include comparisons to baseline.

3.4.1.3 Dosing Period and Measurement Points

This section indicates that ECG data collection should bracket Tmax. In some cases, it may not be practical or possible to collect ECG data before Tmax (e.g., bolus iv infusion, rapid absorption after oral dosing, etc.), especially with non-instrumented conscious animals. The first sentence of the first paragraph in this section should be revised to insert "when possible" prior to "bracketing Tmax."

3.4.1.4 Influence of Heart Rate Change on the QT Interval

The following two items in this section need to be clarified.

1.) This section could be misinterpreted to indicate that correction formula (e.g., Bazett's, etc.) should only be used when heart rate changes are drug related. There are two potential problems with this. First, it is not always apparent if changes in heart rate are drug related. Second, moderate heart-rate changes can occur in some species due to handling (regardless of training) and diurnal influences. This latter point is most pertinent for conscious instrumented animals where ECG data collection can occur for extended periods.

This section should be clarified to avoid misinterpretation.

2.) The penultimate sentence in this section reads "Analyses of QT intervals over a wide range of heart rates can provide more detailed information and increased predictability of the potential effect of a test substance." By itself, the sentence is clear. However, it contradicts the sentence before it which states that corrections for large differences in rates can be misleading; corrections would be required to analyze QT intervals over a wide range of heart rates since baseline data are generally stable. It also is not clear if the sentence is intended to justify cardiac pacing, which is mentioned in the final sentence of this section.

This sentence should be clarified in the context of the surrounding text.

Conclusion

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

Laurie Smaldone, M.D.
Senior Vice President
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MSO Domestic/Documents

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